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| EXAMINER |
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SLOBODYANSKY, ELIZABETH

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| ART UNIT | PAPER NUMBER |
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1652

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
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| 3 MONTHS | 02/13/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/798,339

Applicant(s)

KAKEHI ET AL.

Examiner

Elizabeth Slobodyansky, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 December 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 9 and 11-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9 and 11-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

The amendment filed on December 4, 2006 amending claim 9, canceling claim 10 and adding claims 11-14 has been entered.

Claims 9 and 11-14 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 11 recites "the mutant *purF* gene coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized". Therefore, claim 11 recites the genus of the mutant *purF* genes coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized. These mutants obtained by any mutation resulting in desensitized feedback inhibition by AMP and GMP of a wild type *purF* gene from any source. Thus, claim 11 recites a highly diverse genus of mutant

purF genes coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized defined only by function.

Claim 12 depends from claim 11 and recites "the *guaA* gene and *guaB* gene". Thus, claim 12 recites a highly diverse genus of *guaA* genes and a highly diverse genus of *guaB* genes defined only by function.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification the diverse and variable genus of mutant *purF* genes coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized is represented by a mutant of *Escherichia coli purF* gene in which the lysine residues at position 326 is replaced with a glutamine residue (page 12, lines 12-

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16, for example). The diverse and variable genera of *guaA* genes and *guaB* genes are represented by *E. coli guaBA* operon (page 36, lines 9-16, for example). The specification fails to describe any other representative species of any of the genera by any identifying characteristics or properties other than the functionality of being either a mutant *purF* genes coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized or *guaA* and *guaB* genes. The specification fails to define those structural features of the species that are commonly possessed by members of the genus that distinguish them from others. The specification fails to provide the structure and function correlation common to all members of the genus. Thus, one skilled in the art cannot visualize or recognize the identity of the members of the genus.

Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention at the time of filing.

Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of use of *E. coli purF* gene in which the lysine residues at position 326 is replaced with a glutamine residue and *E. coli guaBA* operon, does not reasonably provide enablement for a method of use of a mutant *purF* gene, including mutant *E. coli purF* gene, coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized having no defined structure and

guaA and *guaB* genes having no defined structure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a mutant *purF* gene, including mutant *E. coli purF* gene, coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized having no defined structure and *guaA* and *guaB* genes having no defined structure because

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the specification does not establish: (A) regions of the protein structure which may be modified without affecting the enzymatic activity encoded by *purF*, *guaA* and *guaB* genes and, in case of *purF*, feedback inhibition; (B) the general tolerance of an encoded enzyme to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any of an enzyme residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The specification provides no guidance as to what are other modifications in *E. coli purF* gene other than Lys326Glu that would result in the requisite desensitization.

Without sufficient guidance, beyond that provided, making a mutant *purF* gene, including mutant *E. coli purF* gene, coding for PRPP amidotransferase of which feedback inhibition by AMP and GMP is desensitized having no defined structure and *guaA* and *guaB* genes having no defined structure is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9, with dependent claims 11-14, recites "gene is decreased". "Gene" cannot be decreased. Gene can be mutated or disrupted resulting in no or decreased 5' nucleotidase activity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 9, 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thaller et al. alone or in view of Cowman et al.

Thaller et al. (form PTO-1449 filed March 12, 2004, reference AAB) teach the sequence of the *aphA* gene (page 193, Figure 1). They further characterize 5'-nucleotidase activity of the *E. coli* AphA enzyme (page 195, Table 1). They teach that another 5'-nucleotidase in *E. coli* is UshA (page 197, 2nd column, last paragraph). They suggest producing strains carrying *aphA* mutations (page 198).

Cowman et al. (form PTO-1449 filed March 12, 2004, reference AAA) teach the *ushA* gene from *E. coli* encoding a 5'-nucleotidase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce *E. coli* mutants having non-functional, for example, disrupted *ushA* gene and *aphA* gene. The motivation to produce such mutants is provided by Thaller et al. who teach 5'-nucleotide dephosphorylating activity of *ushA* gene and *aphA* gene. Mutants with disrupted *ushA* gene and *aphA* gene would have a higher yield of 5'-nucleotides. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because the structures of both *ushA* gene and *aphA* gene were known at the time the invention was made and methods for disrupting known genes were widely used.

Claims 9 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thaller et al. alone or in view of Cowman et al. and further in view of Matsui et al.

The teachings of Thaller et al. and Cowman et al. are outlined above.

Matsui et al. (EP 1004 663 A1, form PTO-1449 filed March 12, 2004, reference AP) teach a method for producing purine nucleosides such as inosine and guanosine which are important as intermediate compounds for synthesis of 5'-inosinic acid and 5'-guanylic acid (page 2, [001], lines 5-7). They teach a microorganism which acquired the purine nucleoside-producing ability because of an increase of an activity of an enzyme involved in the purine nucleoside biosynthesis due to its gene overexpression (page 2, [0007]). They teach that enzyme can be PRPP amidotransferase that is desensitized (page 2, [0008]). They teach the mutation Lys326Glu in PRPP amidotransferase gene (*purF*) resulting in desensitizing the feedback inhibition (page 6, [0055]; page 10,

[0076])) and *E. coli* comprising said mutant PRPP amidotransferase (page 11). They further teach that in order to efficiently utilize the *purF* gene, it can be used with other genes involved in the IMP biosynthesis such as IMP dehydrogenase gene (*guaB*) and GMP synthetase gene (*guaA*) (page 7, [0064]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce *E. coli* mutants having non-functional, for example, disrupted *ushA* gene and *aphA* gene thus preventing the decomposition of inosine 5'-phosphate ester and guanosine 5'-phosphate ester and additional genes such as *purF*, *guaA* and *guaB* that increase their production. The motivation to produce such mutants is provided by Thaller et al. who teach 5'-nucleotide dephosphorylating activity of *ushA* gene and *aphA* gene and Matsui et al. who teach the role of *purF*, *guaA* and *guaB* in the nucleotide biosynthesis. One of ordinary skill in the art at the time the invention was made would have a reasonable expectation of success because the structures of all involved genes were known at the time the invention was made and methods for mutation of known genes were widely used.

Response to Arguments

Applicant's arguments filed December 4, 2006 have been fully considered but they are not persuasive.

With regard to the 103(a) rejection, Applicants argue that "Generally, bacteria have around 5 different types of 5'-nucleotidases. However, the Inventor of the present invention revealed that *E. coli* has only two types of 5'-nucleotidases (*AphA* and

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UshA), encoded by aphA and ushA genes" (Remarks, page 5, last paragraph).

applicants further argue that "it was revealed through the experiment that disruption of either the aphA gene or the ushA gene was not effective in accumulation of IMP, whereas disruption of both the aphA gene and the ushA gene was effective in accumulation of IMP. These results would never have been obvious from Thaller et al. alone or in view of Cowman et al" (page 6, 1st paragraph). This is not found persuasive because it would be obvious to destroy all 5'-nucleotidases genes that result in the decomposition of the desired product. At the time the invention was made it was known that products of two *E. coli* genes, aphA gene or the ushA gene, exhibit 5'-nucleotidase activity. Therefore, it would have been obvious to disrupt these genes. The number of 5'-nucleotidases genes in other bacteria is irrelevant with regard to that. Furthermore, the fact that "disruption of either the aphA gene or the ushA gene was not effective in accumulation of IMP, whereas disruption of both the aphA gene and the ushA gene was effective in accumulation of IMP" does not obviate the rejection because claim 9 requires for both genes, aphA and ushA, to be mutated not just one of them. As discussed above, it would have been obvious to destroy all 5'-nucleotidases genes. In that regard the specification does not produce unexpected results.

The 103(a) rejection over Laird et al is withdrawn in view of Applicants' remarks (page 5). It is agreed that since the 54G2 strain has a purine auxotrophy due to the disruption of purEK gene, it would not be used for the production a nucleoside 5'-phosphate ester.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Tso et al. (April 10, 1982) J. Biol. Chem., Vol. 257, No. 7, pages 3525-3531, describe nucleotide sequence of *Escherichia coli purF* and deduced amino acid sequence of PRPP amidotransferase (GenBank accession J01666).

Tiedeman et al. (July 25, 1985) J. Biol. Chem., Vol. 260, No. 15, pages 8676-8679, describe nucleotide sequence of the *guaA* gene encoding GMP synthetase of *Escherichia coli* K12.

GenBank accession M10101 (April 26, 1993) discloses the nucleotide sequence of *guaA* and *guaB*.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

February 6, 2007